UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,466	10/27/2006	Maria Teresa Flores	14829-003US1 F/USP288389	5995

26161 7590 04/15/2010

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
04/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/564,466	FLORES ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,19-22,25,27-32 and 34-39* is/are pending in the application.

4a) Of the above claim(s) *1-6,8-10,12,20,21,25 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7, 11, 19, 22, 34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 1/29/10, have been entered. Claims 1-12, 19-22, 25, 27-32, 34-39 are pending; claims 13-18, 23, 24, 26, 33 are cancelled; claims 34-39 are newly added; claims 7, 11, 21 are amended; claims 1-6, 8-10, 12, 20, 21, 25, 27-32 are withdrawn; claims 7, 11, 19, 22, 34-39 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group II (claims 7, 11, 13-19 and 22) in the reply filed on 6/16/09 is acknowledged. Applicants continue to traverse the restriction requirement. In particular, Applicants argue that the pending claims share a technical feature, which is reverse-immortalized human OEG cells and that contrary to assertions of the office, this feature is a special technical feature for the reasons provided previously. Applicants argue that the Office reconsider the restriction requirement and cite several passages of the MPEP in support. In particular, MPEP §1850 and 37 CFR 1.475(b)(3). In particular, Applicants argue that the Office's apparent interpretation of certain passages within the MPEP appear to run afoul of PCT Rule 13.3 which states that the determination of Unity of Invention is not affected by the manner of claiming, and that the pending claims are unified and therefore should be examined in concert. See pages 11-15 of the Response.

The Examiner responds firstly that the Restriction requirement has been made final in the prior Office action. Additionally, Applicants' arguments are with regard to whether an invention has unity of invention. In the instant case, the Examiner has provided sufficient guidance to show that unity of invention is not present, because the claimed invention does not make a contribution over the prior art. That is, the technical feature of the claims is considered to be reverse-immortalized human OEG cells, but this technical feature is not considered to be a *special* technical feature, because it does not make a contribution over the prior art

of Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002), which is found below. MPEP §1850 (II) states that, "Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step." The Examiner has provided guidance with regard to why the instant claims do not make a contribution over the prior art, and therefore, do not have a special technical feature. Thus, given that unity of invention does not exist, the claims do not form a single general inventive concept. 37 CFR 1.475 (b) relates to categories of invention that are considered to have unity of invention. In the instant case, because unity of invention is found to be lacking, these categories do not apply to the instant case.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 8-10, 12, 20, 21, 25, 27-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/16/09.

Claim Objections

The objection to claims 7 and 11 is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7, 11, 19 and newly added claims 34-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002).

Response to Arguments. Applicants argue that Salmon teaches methods of immortalization of some cells but does not describe the desimmortalization of reversibly-immortalized cells to obtain functional reverse-immortalized cells, and that their teachings would not have motivated the ordinary skilled artisan to try to obtain reverse-immortalized cells. Applicants argue that Salmon provides guidance using excisable lentiviral vectors in HeLa cells, and thus, the transgene is not an oncogene, and thus, the cells are not immortalized. Applicants argue that the process described in Salmon is not a desimmortalization process, and that further, there is no guidance whether the transfected cells using these vectors maintain their viability and functional properties after the excision of the transgene. Additionally, Applicants argue that Salmon describe the negative effect of excision

of oncogenes in hLSEC immortalized cells, and that immortalized cells have a strict dependence on the presence of immortalizing genes for cell division and only unexcised cells proliferate, so that the cell cycle seems not to be maintained after desimmortalization. See pages 17-18 of the Response.

Applicants argue that Halfpenny does not consider the ability to promote axonal regeneration of OEG cells. In particular, Applicants cite Halfpenny at p. 36, 2nd col., 3rd ¶ and state that this provides guidance to that the skilled artisan would not expect that the immortalized glial cells would be suitable to promote axonal regeneration after transplantation, because the skilled artisan would not have any expectation of repair or regeneration where axonal loss already exists. See p. 18 of the Response.

Response to Arguments. These arguments have been considered but are not persuasive. In particular, Barnett is not used in order to produce reverse immortalized cells. Thus, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to Applicants' arguments to Salmon, the Examiner responds that Salmon provides sufficient guidance and teachings with regard to producing functional reverse-immortalized cells, showing growth arrest of the cells that were immortalized, and then the induction of proliferation of the cells upon transduction of HLox vectors (see Abstract). In fact, Salmon teaches that one major hurdle to stable genetic manipulation of many primary cells is that they fail to divide readily, and that the methods taught by Salmon readily show the ability of lentiviral vectors to transduce cells, regardless of their proliferating status, to obtain conditionally immortalized primary cells, which can then grow robustly in minimal media (see page 405, col. 2, last ¶ and p. 408, col. 1). Applicants' arguments regarding

Salmon's methods not teaching reversible immortalization are not found to be persuasive. Firstly, Salmon describes their methods as an immortalization method. Applicants have not provided any guidance to show that immortalization of cell lines is only defined by oncogenes. In fact, the art readily acknowledges using other genes or vector systems, including the use of telomerase (Salmon, p. 405, col. 1, ¶1), or the lentiviral system that is taught by Salmon. Additionally, Salmon teach using their lentiviral system to include the SV40 large T (Tag) oncogene (Abstract). Applicants have provided no evidence or guidance to show that Salmon's methods, contrary to Salmon's teachings, do not produce immortalized cells.

Applicants' arguments regarding Salmon's teachings regarding the functionality of the resultant cells are not found to be persuasive. In fact, Salmon teaches that it is possible to produce cells that are able to survive more than two weeks in minimal culture (p. 411, col. 1, 1st ¶). Additionally, Salmon teaches that their resultant cell line exhibits the numerous phenotypic markers of the original parent cells (p. 408, col. 1, 1st ¶). Thus, Salmon provide sufficient guidance and a reasonable expectation of success that their methods would produce a cell that would maintain the characteristics of the original parental cells. It is noted that Applicants' claims read on any method of producing immortalized cells, and thus, encompass methods such as those taught by Salmon.

Applicants' arguments regarding Halfpenny's teachings have been fully considered but are not persuasive. In particular, the passage which Applicants cite has been taken out of context. Halfpenny do not teach or suggest that the immortalized glial cells would not be suitable to promote axonal regeneration after transplantation, because the skilled artisan would not have any expectation of repair or regeneration where axonal loss already exists. Rather, Halfpenny teach that the timing of remyelinating treatment is important, because early intervention may offer a significant advantage. Halfpenny do not explicitly or implicitly teach

away from using immortalized glial cells to promote axonal regeneration, they merely caution about the time frame in which to use the cells in transplantation.

Applicants' arguments regarding the teachings of Barnett, Salmon and Halfpenny, have been considered but not persuasive. Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner has provided sufficient guidance with regard to the combination of the references. Accordingly, it is maintained that the combination of Barnett, Salmon and Halfpenny provide a reasonable expectation of success, with sufficient motivation and guidance to arrive at the claimed invention.

Rejection

Barnett teach the isolation and identification of human olfactory ensheathing glial cells (p. 1582, col. 1, Isolation and Culturing of human OECs). Barnett teach the purification of the human OECs (p. 158, 2nd col., Purification of hOEC using L-NGFr and Magnetic Beads). Barnett teach that cells are capable of remyelinating persistently demyelinated CNS axons following transplantation into rat spinal cord (Abstract).

Barnett do not teach that their cells are reversibly immortalized. However, prior to the time of the claimed invention, Salmon teach the reversible immortalization of human primary cells by lentivector-mediated transfer. In particular, Salmon teach utilizing a vector comprising the SV40 large T (Tag) oncogene (Abstract).

Regarding newly added embodiments of claims 34-35, Salmon teach a construct that contains LoP sites, and that the cells were treated with Cre recombinase (Abstract, Figure 1A, *Vectors and Plasmids*, p. 408, col. 1-2).

Regarding claims 36 and 39, Salmon teaches a vector that contains the SV40 large T antigen or human telomerase catalytic subunit (hTERT) (p. 408, *Vectors & Plasmids*). Regarding claims 37-38, Salmon teach that the vector contains thymidine kinase (p. 409, col. 1, Design of Excisable Lentiviral Vectors) and that the cells are sensitive to ganciclovir (p. 409, col. 1, Excision of the Transgene and Conditional Ablation of Unexcised Cells).

Accordingly, in view of the combined art of Barnett and Salmon, it would have been obvious for the ordinary skilled artisan to modify the OEG cells, taught by Barnett, to produce reversibly-immortalized OEG cells, utilizing the methods of Salmon, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to produce reversibly-immortalized OEG cells in order to produce a large number of therapeutic cells for transplantation, as suggested by Salmon (p. 404, Introduction) and further specifically suggested by Halfpenny who teach immortalized cell lines would provide sufficient numbers of cells for transplantation, which could yield large numbers of appropriate cells in homogeneity. See p. 34, col. 2, Immortalised Cell Lines.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 22 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (**Brain**, 123:1581-1588, 2000) when taken with Salmon *et al.* (**Mol. Therapy**, 2(4): 404-414, 2000, IDS) in further view of Halfpenny (**The Lancet Neurology**, 1: 31-40, 2002) as applied to claims 7, 11, 19 and newly added claims 34-39 above, and further in view of Franklin *et al.* (**Glia**, 17: 217-224, 1996). The prior rejection of claim 18 is rendered moot in view of the cancellation of the claim.

Applicants' Arguments. Applicants argue that Franklin describes the use of a retrovirus containing the ts mutant gene of the Tag, but do not excise the oncogene because they argue that the immortalizing gene product is not active

following transplantation into the rat. Applicants argue that nevertheless, it is explained in the present Application that the continued presence of the oncogene in these cells is of concern because it may increase the risk of malignant transformation following transplantation. See page 21 of the Response.

Response to Arguments. Applicants provide the same arguments with regard to Barnett, Salmon and Halfpenny. The Examiner has addressed these arguments above. Applicants' arguments with regard to Franklin are not found to be persuasive. In particular, Franklin is not relied upon with regard to the specific vector they use. Franklin is used with regard to the production of an OEG line. The combined teachings of Barnett, Salmon and Halfpenny provide guidance with regard to the excision of the oncogene.

Rejection

Barnett, Salmon and Halfpenny are discussed above. They do not specifically teach an OEG cell line. However, prior to the time of the claimed invention, Franklin teach the generation of olfactory bulb ensheathing cell lines (p. 218, col. 1, Materials and Methods, Construction of the tsT OBEC Cell line and verification of Clonality).

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to utilize the teachings of Barnett, Salmon and Halfpenny, to produce a reverse-immortalized human OEG cell culture, and then utilize the teachings of Franklin, in order to produce a clonal reverse-immortalized human OEG cell line, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make a cell line in view of Franklin's teachings, who state that, "The reason for using a cell line rather than cells derived from primary culture is that it is difficult to obtain pure populations of the latter that are free from any contaminant phenotype." See p. 218, col. 1, 1st full ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632